Application No. 10/639,948
Confirmation No. 6989

REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claim 1 has been amended. No new matter has been added through the amendment. Claims 1-12 are currently pending. Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §103, and for obviousness-type double patenting.

Examiner's Interview

Applicants thank the Examiner for his time in discussing the pending claims during the recent telephone interview held March 11, 2005. Although no agreement was reached, this reply is submitted in keeping with the comments and discussion of the interview.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejects claims 1 and 4-12 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. The Examiner contends that the scope of the claims is not commensurate with the scope of enablement in the specification. Specifically, the Examiner asserts that the specification does not enable 3-acylated analogues of pyridoxal other than the 3-acylated analogues recited in claims 2 and 3. Applicants traverse.

While not acquiescing to the rejection and in order to expedite prosecution, Applicants have amended claim 1. Applicants have amended claim 1 to recite to recite 3-acylated analogues corresponding to claims 2 and 3. Support can be found throughout the specification, including at paragraphs 12-13.

Rejections Under 35 U.S.C. §103

Claims 1-6, 8-20, 22-25, and 27-41 are rejected under 35 U.S.C. §103(a) for alleged obviousness. The Examiner asserts that claims 1-6, 8-20, 22-25, and 27-41 are unpatentable over Smith et al. (WO 98/19690) in combination with Lobel (U.S. Patent No. 3,282,778) or with DiPiro. The Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three criteria must be met--a suggestion or motivation to combine references, a reasonable expectation of success, and the prior art

reference teaches or suggests all the claim limitations. MPEP §2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has not established a prima facie case of obviousness since there is not expectation of success for the claimed combination.

A. Smith in view of DiPiro

The disclosure of Smith *et al.* in view of DiPiro does not provide an expectation of success. Smith *et al.* do not disclose the use of pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, or any 3-acylated analogue of pyridoxal in the indicated therapy. Only vitamin B_6 and other compounds non-relevant to the present invention are used in Smith *et al.* Although pyridoxal-5'-phosphate, pyridoxal, pyridoxamine and 3-acylated analogues of pyridoxal are derivatives of vitamin B_6 (pyridoxine), they are different compounds, with chemical structures and metabolic properties **distinct** from vitamin B_6. In addition, there is no suggestion in the disclosure of this reference that vitamin B_6 derivatives were contemplated. Indeed, reference is made to "folic acid or a folate or a derivative thereof or betaine or vitamin B_6 or a combination thereof, above, or optionally with vitamin B_{12},...". *See* page 5, lines 9-12. In the case of folic acid or a folate where derivatives thereof are contemplated, a list of such derivatives is specifically disclosed. *See* page 7, lines 1 through 9. This list does not disclose any compounds of the instant application.

Further, vitamin B_6 (pyridoxine) is not pharmaceutically equivalent to the active metabolites. Although there are metabolic pathways from all of the vitamin B_6 precursors to pyridoxal-5'-phosphate, the metabolically active form of the vitamin is not equivalent. For example, the administration of pyridoxine results in high plasma levels of pyridoxine, which can lead to toxic effects such as peripheral neuropathy (Schaumburg *et al.*, *New England J Med* 1983, 309, 445-448). Pyridoxal phosphate itself is less effective than pyridoxal in reducing ischemia induced neuronal damage (Yamashima *et al.*, *Nutr. Neurosci.* 2001, 4(5), 389-397). Pyridoxamine specifically inhibits the formation of advanced end glycation products, which contribute to the chemical modification of proteins during aging and diabetes (Onorato *et al.*, *J. Biol. Chem*, 2000, 275(28), 21177-21784). Pyridoxal-5'-phosphate has been found to alleviate epileptic seizures which do not respond to treatment with pyridoxine (Kuo and Wang, *Pediatr. Neurol.*, 2002, 26(2), 146-7). Since Vitamin B_6 is not pharmaceutically equivalent to the active

metabolites in the instant application, the cited references have not suggested all of the claim limitations.

Additionally, there is no motivation to combine the DiPiro reference with Smith *et al.* The DiPiro reference provides an overview of congestive heart failure and teaches that congestive heart failure can be the result of many causes including hypertension and vasoconstriction. "Hypertrophy of the ventricle ***may*** produce dramatic changes in compliance, even though each individual muscle unit may have relatively normal passive length-tension relations." DiPiro does not disclose the use of pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, or any 3-acylated analogue of pyridoxal in the treatment of congestive heart failure or hypertrophy. In fact, the DiPiro reference teaches away from the instant application. Table 11.3 lists "drugs that may exacerbate or precipitate congestive heart failure." Included in this list are β-blockers (propranolol and others) and calcium channel blockers (verapamil and others). Applicants respectfully assert that the combination of Smith *et al.* and DiPiro would only result from hindsight reconstruction. *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992). There is no motivation to combine Smith *et al.* with DiPiro.

B. Smith in view of Lobel

The disclosure of Smith *et al.* in view of Lobel does not provide an expectation of success. The teachings of Lobel relate to medical preparations for the administration of medicines via oral and parenteral routes, which comprise among other substances, a non-toxic pyridoxine compound. Lobel only presents evidence relating to combining aspirin with a pyridoxine compound for the treatment of colds and combining fluoride with a pyridoxine compound for the treatment of dental carries. Lobel, at best, only provides speculation on the therapeutic advantage of combining a cardiovascular drug with a pyridoxine compound. Lobel does not attribute any medicinal value to pyridoxine derivatives; they simply act as a vehicle to increase the rate of absorption of actual drug. Applicants are the first to show medicinal value from treatment with pyridoxal-5'-phosphate. Therefore, Applicants demonstrate unexpected results over the teaching of Lobel. Further, the combination of pyridoxal-5'-phosphate in combination with other hypertensive agents is a novel treatment method. Applicants respectfully request removal of this rejection.

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In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

Obviousness-Type Double Patenting Rejections

The Examiner has raised an obviousness-type double patenting objection in relation to claims 1 and 46-48 of US 6,339,085 of Haque. The Examiner has also raised a provisional obviousness-type double patenting objection in relation to claims 1-12 and 40-42 of co-pending applicant's Application Serial No. 09/863,093. While not acquiescing to the rejections and in order to expedite prosecution, Applicants submit a terminal disclaimer to obviate the obviousness-type double patenting rejections. Applicants respectfully request removal of the obviousness-type double patenting rejections.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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